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JOINT SYMMETRY IN EARLY AND LATE RHEUMATOID AND PSORIATIC ARTHRITIS

Comparison with a Mathematical Model

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***Objective*. To establish a mathematical model to predict the probability of symmetry of joint involvement as a function of the number of joints involved and to compare expected with actual probabilities in psoriatic arthritis (PsA) and rheumatoid arthritis (RA) and in early and late disease.**

***Methods*. Random involvement of joints was assumed, and the binomial theorem was used to give the frequency distribution of involved joints as a function of each joint count. Ten joint pairs were included: shoulder, elbow, wrist, metacarpophalangeal joints, proximal interphalangeal (PIP) joints of the hands, hip, knee, ankle, metatarsophalangeal joints, and PIP joints of the feet. Observed probabilities were obtained from subjects with early (duration ≤12 months) and late PsA and RA.**

***Results*. The number of subjects in each of the disease subgroups was as follows: early PsA n = 33, late PsA n = 77, early RA n = 61, late RA n = 93. Observed probabilities of symmetry exceeded predicted probabilities for all disease subgroups. The median number of involved joints in each group was as follows: early PsA 4, late PsA 8, early RA 8, late RA 15 (χ^2 = 95.3, 3 degrees of freedom, P = 0.0001, by Kruskal-Wallis test). After correcting for the discrepancy in the number of involved joints, no difference in joint symmetry was found between the groups (χ^2 = 1.77, P = 0.62 by Friedman two-way analysis of variance). Similar results were obtained when individual hand and foot joints were analyzed separately.**

***Conclusion*. The pattern of joint involvement is often used to distinguish between rheumatoid and psoriatic arthritis. This study confirms that symmetry is largely a function of the total number of joints involved and that, in terms of joint pattern, differences between these disorders are more quantitative than qualitative. Both disorders have high absolute values of symmetry, particularly in the joints of the wrist and hand.**

In 1973 Moll and Wright described 5 clinical subsets of psoriatic arthritis (PsA). Of these 5 subsets, they described the most common group as an asymmetric oligoarthritis (60%), followed in frequency by symmetric polyarthritis (30%) (1). Subsequent surveys have shown the most common clinical subset of PsA to be a symmetric polyarthritis resembling rheumatoid arthritis (RA), occurring in some 70% of cases (2,3). The usual definition of symmetry requires that at least 50% of involved joints are symmetric pairs (3). Given this definition, and given that there are a finite number of possible joints that can be involved, it has been argued that the presence of symmetry is strongly influenced by the total number of joints involved (3). However, it seems likely that symmetry is much more than a random event, and a number of reasons have been put forth to explain the occurrence of matched joint pairs in inflammatory arthritis (4).

The aims of the present study were 1) to establish a mathematical model that could be used to predict the probability of symmetry as a function of the number of joints involved, using both random and nonrandom constraints, 2) to compare observed and expected probabilities in early and late RA and PsA, and 3) to compare the observed probabilities across disease sub-

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Table 1. Worked example for n = 7*

Column A, term from binomial expression	Column B, product of term in column A, given a = b = 0.5	Column C, probability of match, p†	Column D, probability of 2 matches‡	Column E, column B × column D
$21a^5b^2$	0.164	5/10 = 0.5	0.5 × 0.5 = 0.25	0.164 × 0.25 = 0.0410
$35a^4b^3$	0.273	4/10 = 0.4	0.4 × 0.4 = 0.16	0.273 × 0.16 = 0.0437
$35a^3b^4$	0.273	4/10 = 0.4	0.4 × 0.4 = 0.16	0.273 × 0.16 = 0.0437
$21a^2b^5$	0.164	5/10 = 0.5	0.5 × 0.5 = 0.25	0.164 × 0.25 = 0.0410
Total§				0.1694

* As seen in this example, the overall probability of symmetry is 0.1694.
† Maximum probability of a joint being involved on either side (given by maximum value of the index in column A).
‡ Given probability of 1 matched pair, p (column C), probability of 2 matched pairs is given by p × p.
§ Overall probability of symmetry, or p(s).

groups while correcting for the number of involved joints. We compared predictions from the model with the reality of joint symmetry in patients with PsA and RA who were seen in a clinic for patients with early arthritis and with patients with more established disease who were seen in rheumatology outpatient clinics.

PATIENTS AND METHODS

Mathematical model. We assumed chance involvement of joints and used the binomial theorem to give the frequency distribution. The assumptions of the model were as follows: 1) All joints have an equal chance of involvement; 2) The binomial distribution is appropriate to predict frequency of joint involvement; 3) Symmetry is defined by (number of joints as symmetric pairs/total number of joints) ≥ 0.5; 4) 10 defined joint pairs considered: (shoulder, elbow, wrist, metacarpophalangeal [MCP] joints, proximal interphalangeal [PIP] joints of the hands, hip, knee, ankle, metatarsophalangeal [MTP] joints, and PIP joints of the feet); 5) Distal interphalangeal (DIP) joints excluded (because this feature is much more common in PsA and the pathogenesis of DIP involvement may differ between the disorders [5]).

The binomial theorem sets out the probability distribution of 2 complementary events with probabilities a and b, the probability being given by the expansion $(a + b)^n$. This distribution, which approximates to the normal distribution as n increases and a = b = 0.5, underlies statistical applications such as the chi-square test. The expansion is given by:

$$(a + b)^n = {}^nC_n a^n + {}^nC_{n-1}a^{n-1}b + \ldots + {}^nC_r a^r b^{n-r} + \ldots {}^nC_1 ab^{n-1} + {}^nC_o b^n$$

where a + b = 1

The coefficients of expansion (nCr) are given by:

$${}^nC_r + \{n!\}/\{r!\}\{n - r\}!$$

However, the coefficients up to n = 100 are given in standard reference texts (6). As an example, for n = 2, the coefficients are 1, 2, and 1. This gives the following familiar solution:

$$(a + b)^2 = a^2 + 2ab + b^2$$

Given that a and b can be taken to represent the right or left side, the frequency of observed events for (n = 2) will be in the ratio of 1:1 for bilateral or unilateral occurrence, respectively. The probability of an event occurring on the left or right is assumed to be equal, so a = b = 0.5. The sum of each of the terms is equal to unity ($[0.5^2] + [2 \times 0.5 \times 0.5] + [0.5^2]$). Since we are only interested in matched pairs, the first and last terms are not required, and the probability of a single pair is given by (2 × 0.5 × 0.5 = 0.5).

Once this probability has been determined, the probability of a matched pair, p, must be calculated. Assuming a set of 20 joints (10 on either side), the probability of a joint being involved on either side for n = 2 is 2/20 = 0.1. Therefore, given a single joint involvement on one side, the probability of a matching joint on the opposite side is 0.1. The overall probability of symmetry, p(s), is given by 0.5 × 0.1 = 0.05.

To summarize these steps: For n = 2, 1 symmetric pair is required (by definition). Binomial coefficients for n = 2 are $a^2 + 2a^1b^1 + b^2$. Given a = b = 0.5, then $2a^1b^1 = 2 \times 0.5 \times 0.5 = 0.5$. Probability, p, of a single joint being involved on either side = 2/20 = 0.1. Therefore, the overall probability of symmetry is given by: p(s) = 0.5 × 0.1 = 0.05 (or 1 in 20).

For n = 7, two matched pairs are required to fulfill the definition of symmetry. The terms for n = 7 are given below and in the calculations in Table 1. For n = 7, binomial coefficients (relevant combinations in italics) are:

$$1a^7b^0 + 7a^6b^1 + \textit{21}a^5b^2 + \textit{35}a^4b^3 + \textit{35}a^3b^4 + \textit{21}a^2b^5 + 7a^1b^6 + 1a^0b^7$$

The process is repeated for values of n from 2 to 13. For n values ≥14, all cases are symmetric.

Clinical findings. All the data used in this study were collected in rheumatology outpatient clinics in Leeds, Bradford, and Milan, according to a standard protocol. We defined early arthritis as a disease duration of ≤12 months. PsA was defined as a persistent inflammatory arthritis of at least 1 peripheral joint in a person with psoriasis (or a confirmed history of psoriasis) and the absence of rheumatoid factor. RA was defined by the 1987 revised criteria of the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) (7). For late disease, the initial data were collected on consecutive patients with PsA in Leeds, Bradford, and Milan. Patients with RA were selected from Bradford. The male:female ratio in the PsA group showed a small selection bias in favor of males, although the male:female ratio was still less than unity. Patients with early disease were selected consecutively in early arthritis clinics.

In all patients, information on joint tenderness or

Table 2. Demographic characteristics of the study patients by disease group*

	Early PsA	Late PsA	Early RA	Late RA
Age, years†	32.2 (15–73)	53 (23–76)	55.2 (15–87)	60 (30–81)
No. female/no. male	13/20	29/48	46/15	57/36
Duration of disease, years	0.5 (0.12–1.0)	14.4 (1.5–59.0)	0.42 (0.1–1.0)	10.0 (1.5–53.0)
Seropositive, no. (%)	0	0	39/58 (67)	67/79 (85)

* PsA = psoriatic arthritis; RA = rheumatoid arthritis.
† Median (range).

swelling of the shoulders, elbows, wrists, all MCP joints, all PIP joints of the hand, knees, ankles (tibiotalar), all MTP joints, and PIP joints of the foot was recorded; pain on movement was recorded for hip joints. In patients with established disease, swelling, tenderness, deformity, and limited range of motion were recorded for the above joint groups. For both early and late arthritis, *any* positive finding was coded as joint involvement.

Symmetry was defined as for the mathematical model. Oligoarthritis was defined as ≤4 joints, polyarthritis as ≥5.

Statistical analysis. All statistical comparisons were performed using nonparametric tests. In order to compare the relationship between probability of symmetry, i.e., p(s), and number of joints involved, the area under each curve was calculated using the trapezium rule. Occasionally, when a disease group had a void in the number of joints involved, the value was obtained by interpolation. Statistical comparisons of the areas were performed using the Friedman two-way analysis of variance (ANOVA).

RESULTS

Demographic features. Demographic characteristics of the patients by group are shown in Table 2. Of the late PsA group, 44 patients were from Milan and the others from the Leeds area. On average, the PsA patients were younger than the RA patients, but the late PsA group had a longer duration of disease compared with late RA group. Each of the PsA groups had more males than females, in contrast to the RA groups.

Joint involvement and pattern. Table 3 provides data on the pattern of joint involvement, by disease group. Most cases were classified as symmetric polyarthritis, with only a few being classified as asymmetric polyarthritis. Asymmetric oligoarthritis occurred predominantly in the patients with PsA. The most frequent pattern found in each group was symmetric polyarthritis, except in the early PsA group, where the most frequent pattern was symmetric oligoarthritis (39%).

The total number of joints involved for each disease group was as follows: early PsA median 4 (range 1–20), late PsA median 8 (range 1–20), early RA median 8 (range 2–16), late RA median 15 (range 2–20) (Table 4). These differences were significant when compared by Kruskal-Wallis test ($\chi^2 = 95.3$, $P = 0.0001$). This is reflected in Table 5, which shows the frequency of involvement of individual joints by disease group. For all disease groups, the wrists, MCP joints, and PIP joints of the hand were most frequently involved and had the highest number of symmetric pairs. In early PsA, the small joints of the foot were infrequently involved, whereas in early RA about one-third of the patients had MTP joint involvement.

Mathematical model and observed probabilities. The observed probability of joint symmetry for the combined disease groups, and the probability of joint symmetry as predicted by the model, are shown in Figure 1. The predicted probability showed a general increase with number of involved joints, but the increase was not linear, nor was it always sustained. This saccadic pattern results from the mathematical definition used to define symmetry. When the number of involved joints

Table 3. Classification of joint involvement pattern by disease group*

	Oligoarthritis		Polyarthritis	
	Asymmetric	Symmetric	Asymmetric	Symmetric
Early PsA (n = 33)	9 (27)	13 (39)	1 (3)	10 (30)
Late PsA (n = 77)	9 (12)	10 (13)	3 (4)	55 (71)
Early RA (n = 61)	1 (2)	10 (16)	2 (3)	48 (79)
Late RA (n = 93)	2 (2)	5 (5)	1 (1)	85 (91)

* Values are the number (%). PsA = psoriatic arthritis; RA = rheumatoid arthritis.

Table 4. Median number of involved joints by disease group*

	Early PsA (n = 33)	Late PsA (n = 77)	Early RA (n = 61)	Late RA (n = 93)	P†
All joints					
Median	4 (2)	8 (3)	8 (7)	15 (3)	0.0001
Range	1–20	1–20	2–16	2–20	
Hands only					
Median	4 (0)	7 (2)	11 (4)	18 (9)	0.0001
Range	0–20	0–20	0–20	0–20	
Feet only					
Median	1 (0)	7 (3)	1 (0)‡	18 (9)	0.0001
Range	0–20	0–20	0–20‡	0–20	

* For "all joints," the joints of the hands (metacarpophalangeal, proximal interphalangeal [PIP]) and the joints of the feet (metatarsophalangeal, PIP) were counted as 1 joint. For "hands only" and "feet only," the individual joints of the hands and feet were counted. Values in parentheses are the number of symmetric pairs. PsA = psoriatic arthritis; RA = rheumatoid arthritis.
† All disease groups, compared by Kruskal-Wallis test.
‡ Based on 11 cases.

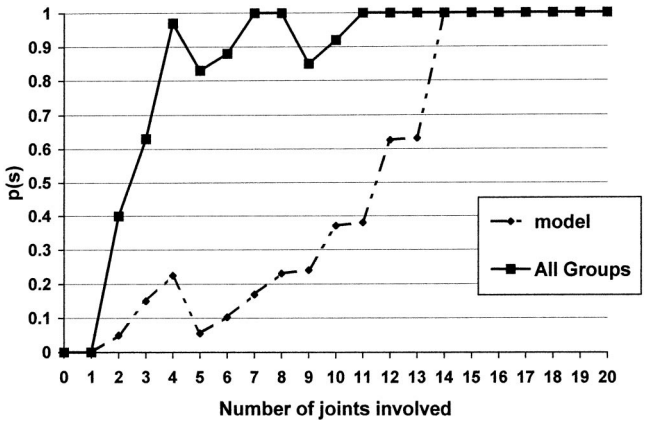

Figure 1. Probability of symmetry, or p(s), as a function of the number of joints involved, for the model and for the combined disease groups.

exceeded 13, all cases were symmetric, since the model is constrained to a total of 20 joints. The observed probability exceeded the predicted probability at each joint frequency up to 13 for the combined disease groups.

Figure 2 shows the observed probabilities for each disease group. The total area under the curve for each group (median, range of values from trapezium rule) was as follows: early PsA 15.59 (1.0, 0.25–1.0), late PsA 16.83 (1.0, 0.64–1.0), early RA 17.18 (1.0, 0.5–1.0), late RA 16.76 (1.0, 0.25–1.0). These areas were not statistically significantly different ($\chi^2 = 1.77$, $P = 0.62$ by Friedman two-way ANOVA).

The parameter p of the model was manipulated in order to obtain a better "fit" for the predicted probabilities. Instead of using chance (model A), the probability of finding a matched pair was increased by first using an aggregate probability of symmetry from the clinical data (0.77; model B), and second, when the observed and expected frequencies were still discrepant, a probability of 0.9 (model C). The results of these manipulations of the model are presented in

Table 5. Frequency of joint involvement by disease group*

	Early PsA (n = 33)	Late PsA (n = 77)	Early RA (n = 61)	Late RA (n = 93)	All patients (n = 264)
R shoulder	2 (6)	27 (35)	19 (31)	63 (68)	112 (42)
L shoulder	6 (18)	23 (30)	17 (28)	68 (73)	116 (44)
R elbow	3 (9)	18 (23)	13 (21)	58 (62)	93 (35)
L elbow	5 (15)	17 (22)	12 (20)	60 (65)	96 (36)
R wrist	9 (27)	45 (58)	42 (69)	85 (91)	184 (70)
L wrist	7 (21)	42 (55)	42 (69)	83 (89)	176 (67)
R MCPs	15 (45)	53 (69)	49 (80)	83 (89)	207 (78)
L MCPs	15 (45)	45 (58)	46 (75)	85 (91)	198 (75)
R PIPs, hand	14 (42)	45 (58)	46 (75)	75 (81)	185 (70)
L PIPs, hand	16 (48)	42 (55)	46 (75)	73 (78)	183 (69)
R hip	4 (12)	8 (10)	5 (8)	27 (29)	44 (17)
L hip	3 (9)	13 (17)	5 (8)	22 (24)	43 (16)
R knee	11 (33)	34 (44)	31 (51)	74 (80)	151 (57)
L knee	14 (42)	29 (38)	24 (39)	66 (71)	135 (51)
R ankle	9 (27)	30 (39)	28 (46)	64 (69)	133 (50)
L ankle	9 (27)	29 (38)	21 (34)	57 (61)	118 (45)
R MTPs	12 (36)	54 (70)	22 (36)	76 (82)	167 (63)
L MTPs	16 (48)	51 (66)	22 (36)	73 (78)	166 (63)
R PIPs, foot	4 (12)	31 (40)	2/11 (18)	64 (69)	101/214 (47)
L PIPs, foot	6 (18)	28 (36)	2/11 (18)	63 (68)	99/214 (46)

* Values are the number (%). PsA = psoriatic arthritis; RA = rheumatoid arthritis; R = right; L = left; MCPs = metacarpophalangeal joints; PIPs = proximal interphalangeal joints; MTPs = metatarsophalangeal joints.

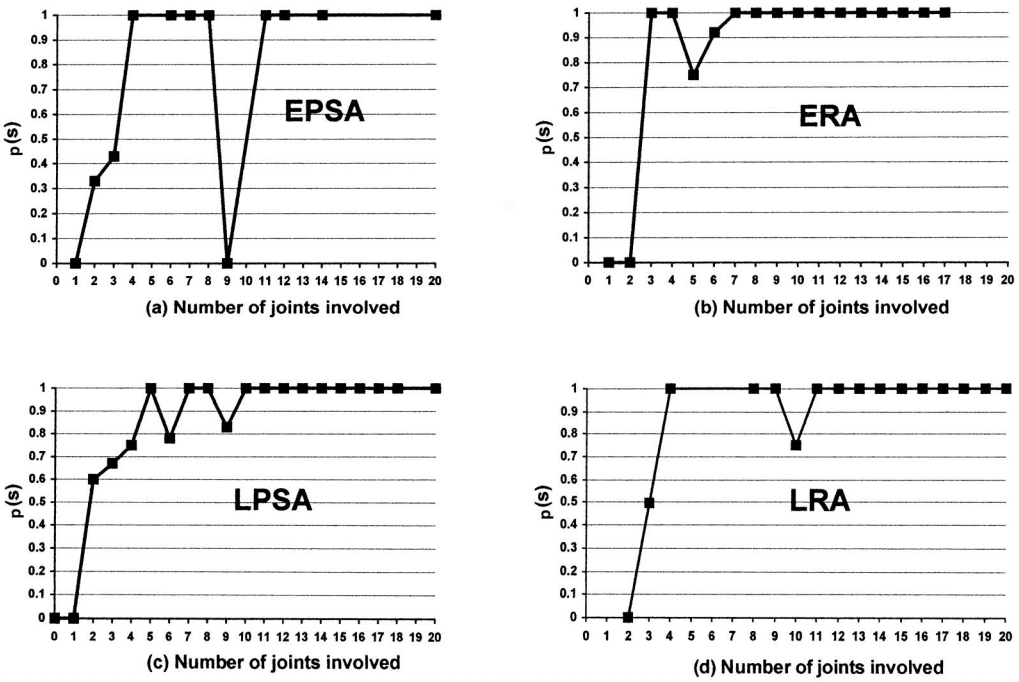

Figure 2. Probability of symmetry, or p(s), as a function of the number of joints involved, by disease group. **a,** Early psoriatic arthritis (EPSA). **b,** Early rheumatoid arthritis (ERA). **c,** Late psoriatic arthritis (LPSA). **d,** Late rheumatoid arthritis (LRA). Note that for some of the joint frequencies there is a void where none of the patients had that number of joints involved. Actual data points are shown; the graphs are interpolated.

Figure 3. As seen in this figure, the predicted probabilities were still less than the observed data. The area under the curve was calculated for the combined groups (as in Figure 1) and compared with the predicted probabilities, and the results, presented as the total area (median, range of values from trapezium rule), were as follows: combined groups 16.48 (1.0, 0.4–1.0), model A 8.93 (0.29, 0.06–1.0), model B 13.01 (0.69, 0.39–1.0), model C 14.73 (0.82, 0.56–1.0) (χ^2 = 26.46, P = 0.0001 by Friedman two-way ANOVA).

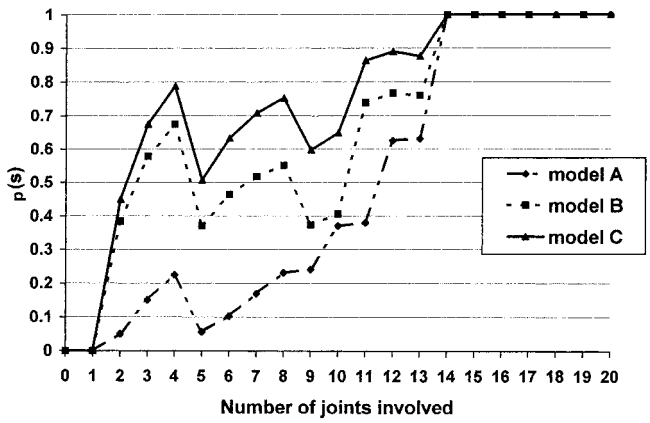

Figure 3. Probability of symmetry, or p(s), for 3 different values of p, the probability of obtaining a matched pair. Model A, p = chance; model B, p = 0.77; model C, p = 0.9.

Separate analysis of hands and feet. Because the small joints of the hands and feet were counted collectively in the main model, these joints were subsequently analyzed separately. For both hands and feet, of the total of 20 MCP (or MTP) and PIP joints, the median number of involved joints in each group is shown in Table 4. Due to missing data in the early RA group, the data for the feet are based on 11 cases only. Area under the curve for the hands, presented as the total (median, range of values from trapezium rule), was as follows: early PsA 13.26 (1.0, 0–1.0), late PsA 14.93 (1.0, 0.17–1.0), early RA 15.43 (1.0, 0.38–1.0), late RA 15.37 (1.0, 0.25–1.0) (χ^2 = 1.65, P = 0.65 by Friedman two-way ANOVA). The area under the curve for the data relating to the feet was not calcu-

lated because there were too many missing data points.

DISCUSSION

The purpose of a mathematical model is to represent a physical situation in mathematical terms, so that it becomes possible to explain the behavior of, and to make predictions about, the physical circumstance. It is clear from the clinical data that joint involvement in RA and PsA is not just a matter of chance and that some joints (and joint pairs) are more likely to be involved than others. The model, although unable to reflect the observed situation, has provided a reference with which observed probabilities of symmetry can be compared.

The model has also indicated a way of presenting the data in such a way that the symmetry of these diseases can be compared statistically. Since the definition of symmetry is based on a proportion (see assumptions of the model) and since symmetry is described in a finite set of joints, then the greater the number of joints involved the higher the chance of these joints being described as symmetric. Calculating the area under the curve of the probability of symmetry at each joint frequency for each condition allows for any discrepancy in the number of joints involved. The results of this study have shown that rheumatoid and psoriatic arthritis differ in the absolute number of involved joints but are equally symmetric when this correction is applied. The differences in symmetry between early and late disease, observed in this study and in a study by Jones et al (8), merely reflect the differences in number of joints involved. In clinical practice, of course, we see more asymmetric oligoarthritis in PsA, but it is, strictly speaking, incorrect to call PsA a less symmetric disease than RA. These observations are equally valid if the joints of the hand and feet are analyzed individually, although the difference in number of joints involved between disease subsets is, perhaps, even greater (see Table 4).

Most prominent among the reasons proposed for symmetry of joint involvement are the neural theories (4). In animal models, inflammatory responses on one side elicit comparable changes on the opposite side, an effect that is blocked by cutting the peripheral nerve to the opposite limb. This effect is seen in humans when a person has both an inflammatory arthritis and a unilateral neurologic lesion such as hemiplegia. The sympathetic nervous system may also be involved as unilateral sympathetic blockade improves the pain and inflammation of inflammatory arthritis. However, some questions remain unanswered. Is synovitis in one finger usually matched by synovitis in the opposite finger, or can other inflammatory responses occur? Can dactylitis elicit a similar response in the contralateral digit? Clinical experience would suggest otherwise. Why are the joints most commonly involved in RA and PsA the wrists, MCP joints, and PIP joints—is this more related to physical factors such as frequency of joint use, and do these physical factors better explain the symmetry?

The definitions of disease used in this study, although accepted, are likely to lead to some overlap between RA and PsA. Indeed, it is likely that many of the cases labeled as PsA in this study would fulfill the ACR criteria for rheumatoid (albeit seronegative) arthritis. This may partly explain the increase in the frequency of the symmetric polyarthritis subset of PsA (15% in the original descriptions by Moll and Wright [1] to 68–78% in more recent published series [3,9]), particularly if cases positive for rheumatoid factor are included (2). Without other distinctive features such as inflammatory changes in the DIP joints or features of a seronegative spondylarthropathy (such as enthesitis, dactylitis, sacroiliitis, spondylitis, and iritis) the distinction between RA and PsA becomes difficult. Other radiologic findings (such as osteosclerosis, new bone formation, and ankylosis) that are features of PsA and have been shown to distinguish between seronegative and seropositive RA (10) may also be helpful in disease designation.

There is a need for a more distinctive set of diagnostic criteria for PsA—criteria that reflect the underlying pathophysiology of the disorder. It has recently been postulated that the primary site of inflammation in PsA is extrasynovial and that synovial inflammation may be a secondary phenomenon in this condition (5). A mandatory criterion of definite enthesitis (either peripheral or axial) added to the existing criteria of persistent inflammatory arthritis, psoriasis, and seronegativity would provide greater specificity for PsA. However, application of this criterion would have eliminated many of the cases labeled as PsA in the present study. Further work is needed on composite criteria of the kind originally suggested by Bennett (cited by Oriente et al [11]), where, in addition to the obligatory features of arthritis and psoriasis, a defined number of other features are required; these include enthesopathy, dactylitis, DIP joint involvement, spinal involvement, seronegativity, and absence of subcutaneous nodules.

The criteria for joint involvement that were used in this study (tenderness on palpation, swelling, deformity, or limited range of motion) are likely to yield higher frequencies of joint involvement than other criteria requiring only joint swelling or deformity. These criteria were uniformly applied across the study population, thereby avoiding bias in favor of one disease group. However, it is likely that our method of determining joint involvement led to an underestimate since other studies, using modern imaging techniques (12), have shown frequent subclinical involvement. Had we used these other, more sensitive, methods of detecting articular involvement, it is possible that the observed differences in total number of involved joints would have diminished. Indeed, articular involvement may be universal in these disorders, the clinical pattern merely reflecting different degrees of inflammation.

In summary, the pattern of joint involvement is often used to distinguish between RA and PsA. The results of this study confirm that symmetry is largely a function of the total number of joints involved and that, in terms of joint pattern, differences between these disorders are more quantitative than qualitative. Both disorders have high absolute values of symmetry, particularly in the joints of the wrist and hand. Cases of seronegative arthritis with psoriasis may be incorrectly labeled as PsA unless other distinctive features of PsA are found. Further work is needed to improve diagnostic criteria for PsA.

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